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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/757,077	01/14/2004	Lance E. Steward	17355CIP3(BOT)	5352

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ALLERGAN, INC.
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IRVINE, CA 92612-1599

EXAMINER

HAYES, ROBERT CLINTON

ART UNIT	PAPER NUMBER
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1649

MAIL DATE	DELIVERY MODE
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08/09/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/757,077

Applicant(s)

STEWART ET AL.

Examiner

Robert C. Hayes, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 May 2007.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-3 and 45-52 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3 and 45-52 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4/28/04/7. 6) ☒ Other: *1x ref.*

DETAILED ACTION

Sequence Rules

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). See enclosed error report, which requires only changing <125. and <223>, as indicated. Note further that page 13 line 26 was not addressed for the 4 amino acid sequence, in which SEQ ID NOs: 14 & 15 end with NYKD, versus MYKD.

Note that failure to fully respond to both the requirements for sequence compliance and the office action below will be held as *nonresponsive*, and will result in *abandonment* of this application. Note further that a new CRF, paper copy and appropriate statement that these are the same and no new matter exists is still required.

Election/Restrictions

2. Applicant's election of Group I (claims 1-18 & 30-44, as it relates to botulinum toxin A) in the reply filed on 1/01/06 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims directed to any different modified neurotoxin are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 11/01/06. It is noted that the amended claims are now directed toward only modified botulinum toxin A.

Information Disclosure Statement

3. The information disclosure statement filed 4/28/04 fails to fully comply with 37 CFR 1.98(a)(2), which requires a *legible copy* of each U.S. and foreign patent; each *publication* or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered, for those references crossed-out. Note duplicate citations are also crossed-out,

Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C(1).

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 & 45-52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

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No proper antecedent basis nor conception in context with that described within the specification at the time of filing the instant application is apparent for a modified botulinum type A “comprising at least one additional amino acid sequence comprising SEQ ID NO: 27”, especially as it relates to “increas[ing] biological persistence...” (i.e., as it relates to base claims 1-3). In contrast, the specification solely describes on page 71 “a recombinant construct with *both* the eight amino acid residues of SEQ ID NO: 27 (PFV NKQFN) deleted from the N-terminus *and* the twenty-two amino acid residues of SEQ ID NO: 28... deleted from the C-terminus of the light chain of botulinum toxin A exhibits *reduced activity*... [emphasis added]”. No other description appears to exist. In other words, the sole description of a construct with a deletion of SEQ ID NOs: 27 & 28 is not reasonably equivalent to the claimed conception of “comprising at least one additional amino acid sequence comprising SEQ ID NO: 27” for any purpose; thereby, constituting new matter.

Accordingly, no proper antecedent basis nor conception in context with that described within the specification at the time of filing the instant application then reasonably exists for the broader recitations of “further comprising at least one additional leucine-based motif” (i.e., as it relates to claims 45-50), or “further comprising at least one additional tyrosine-based motif” (i.e., as it relates to claims 51-52); thereby, also constituting new matter. No such basis exists in the original claims, nor exists in *pps* 27, 33, 38, 39, 40, 53, 109, 111-118, 125, 140, 141, 275, 277, 284, 285, 288, 291-298, or Examples 4, 6 & 11, in contrast to Applicants’ assertions.

Lastly, no proper antecedent basis nor conception in context with that described within the specification at the time of filing the instant application is apparent for broadening the “at least one amino acid” in base claim 45a to any “acidic amino acid”, versus only to glutamate or

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aspartate, as alternatively described in *pp* 0033 of the specification; thereby, constituting new matter. No such basis exists in *pps* 27, 33, 39, 53, 109, 125, 288, or Examples 4, 6 & 11, in contrast to Applicants' assertions.

5. Claims 1-3 & 45-52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for specific modified BoNT/A neurotoxin proteins with a definable sequence change and recited definable and assayable function, does not reasonably provide enablement for any structurally and functionally uncharacterized modified BoNT/A molecules. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Pages 10-11 of the specification mention "leucine-based motifs" and separately mention "tyrosine-based motifs" in modified botulinum neurotoxins, which supposedly can increase biological half-life, or increase their biological activity (e.g., pages 4-5 & 7). Page 71 of the specification solely describes "a recombinant construct with **both** the eight amino acid residues of SEQ ID NO: 27 (PFV NKQFN) deleted from the N-terminus **and** the twenty-two amino acid residues of SEQ ID NO: 28... deleted from the C-terminus of the light chain of botulinum toxin A exhibits *reduced activity*... [emphasis added]". No specific examples of increased biological activity using any specific and structurally definable "leucine-based motif" or "tyrosine-based motif" modified BoTx/A toxin related to adding a sequence comprising SEQ ID NO: 27 are disclosed, even though Example 4 prophetically and generically mention that botulinum

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neurotoxins can be modified to include “a leucine-based motif and/or additional tyrosine-based motifs”. No other guidance is provided within the instant specification.

The first problem is that is unknown what specific function is envisioned that a “modified” BoTx/A neurotoxin is expected to possess (i.e., as it relates to undefined “biological persistence[s]” recited in base claims 1, 45 & 51). Second, it is unknown what function, if any, a “modified BoTx/A neurotoxin actually possesses, beyond comprising an “*additional* leucine-based motif” or an “*additional* tyrosine-based motif” of unknown sequence and function, in order for one skilled in the art to reasonably known how to make and use the instant invention, without requiring undue experimentation to determine such.

In other words, the terms “modified botulinum neurotoxin type A”, “additional tyrosine-based motif”, “leucine-based motif”, “SEQ ID NO: 27, and “increase biological persistence” by themselves set forth little structural and functional characteristics. The specification does not teach which particular amino acids are critical for any “modified” neurotoxin function, as it relates to any “tyrosine-based motif” assayable function or to any “leucine-based motif” BoTx’s function, etc. Nor does the specification teach how to distinguish such modified BoTx/A analogs encompassed by the instant invention from any different BoTx/A-related polypeptide that possesses none of the desired functions of the instant invention. In contrast, any such broadly claimed polypeptides without definable structural and functional characteristics would be expected by the skilled artisan to encode inactive proteins. For example, Rudinger states on page 3 that “it is impossible to attach a unique significance to any residue in a sequence. A given amino acid will not by any means have the same significance in different peptide sequences, or even in different positions of the same sequence”. Rudinger further states on page 6 that “the

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significance of particular amino acid sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study". Therefore, the lack of guidance provided in the specification as to what minimal structural requirements are necessary for a functional modified BoTx/A polypeptide would prevent the skilled artisan from determining whether any random modification or mutation to a BoTx/A molecule could be made which retains the desired function of the instant invention, because any random mutation or modification manifested within a modified BoTx/A polypeptide would be predicted to adversely alter the biologically active 3-dimensional conformation of the polypeptide, without requiring undue experimentation to determine otherwise.

It is suggested that amending the claims to recite a distinguishable and assayable function, such as increased half-life, as well as structurally define what exactly constitutes a tyrosine-based motif and a "leucine-based motif", etc., etc., all as it relates to the BoTx neurotoxin type A well known in the art, may obviate part of this rejection.

6. Claims 1, 3 & 45-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite and incomplete for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is ambiguous what exactly constitutes a "increased biological persistence" or "increased in biological activity" when no such activity is recited in the claims, nor defined with closed language within the specification.

Claim 3 further lacks proper antecedent basis for the recitation of "wherein the modified terminal end is a N-terminus", because no such modification now exists in base claim 1.

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Conclusion

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Robert Hayes whose telephone number is (571) 272-0885. The examiner can normally be reached on Monday through Thursday from 9:00 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached on (571) 272-0841.. The fax phone number for this Group is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

A handwritten signature in black ink, appearing to be 'RCH' with a checkmark-like flourish at the end.

Robert C. Hayes, Ph.D.
July 26, 2007

ROBERT C. HAYES, PH.D.
PRIMARY EXAMINER

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Sequence Listing could not be accepted due to errors.

See attached Validation Report.

If you need help call the Patent Electronic Business Center at (866)
217-9197 (toll free).

Reviewer: Anne Corrigan

Timestamp: Wed Jun 13 13:43:27 EDT 2007

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Reviewer Comments:

<210> 125

<211> 20

<212> PRT

<213> Clostridium botulinum serotype D

<220>

<221> CONFLICT

<222> (1)...(20)

<223>

Variant of amino-terminal 30 amino acids of LC

Please move the above text to the <223> line, since it is the <223>
response. Same error in Seq. 128.
